

Gestagens with an  $\alpha$ -hydroxyketone structure in the side chain are subject to an acyloin rearrangement during storage. In this case, steric variants occur. This rearrangement is

accelerated by many pharmaceutical adjuvants (e.g., lactose, magnesium stearate).

Moreover, oxidation reactions occur in various molecular positions.

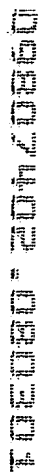
### Object and Solution

The object is thus to protect gestagens, especially (21S)-21-hydroxy-21-methyl-14,17-ethano-19-norpregna-4,9,15-triene-3,20-dione, from decomposition by acyloin rearrangement or oxidation without having a negative effect on the pharmacological compatibility and pharmaceutical processing.

The object is achieved by a combination that consists of at least one gestagen and a  $\beta$ -cyclodextrin or  $\gamma$ -cyclodextrin, or derivatives of these cyclodextrins, which are obtained by etherification or esterification of free alcoholic functions of the cyclodextrins, whereby the gestagens are 14,17-C<sub>2</sub>-bridged steroids, which belong

FOE030" 20420360

**SECRET**



**SECRET**

**SECRET**

- SECRET**

$R^7$  stands for an  $\alpha$ - or  $\beta$ -position  $C_1$ - $C_4$  alkyl radical, whereby then  $R^6$  and  $R^{6'}$  represent hydrogen atoms, or else

$R^6$  and  $R^7$  together stand for an  $\alpha$ - or  $\beta$ -position methylene group, and  $R^{6'}$  stands for a hydrogen atom, or

$R^6$  and  $R^{6'}$  together stand for an ethylene group or a methylene group, and  $R^7$  stands for a hydrogen atom,

$R^9$  and  $R^{10}$  in each case stand for a hydrogen atom or a common bond,

$R^{11}$  and  $R^{12}$  in each case stand for a hydrogen atom or a common bond,

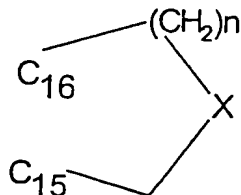
$R^{13}$  stands for a methyl or ethyl group,

$R^{15}$  stands for a hydrogen atom or a  $C_1$ - $C_3$  alkyl radical,

$R^{16}$  and  $R^{16'}$ , independently of one another, stand for a hydrogen atom, a  $C_1$ - $C_3$  alkyl radical or a  $C_2$ - $C_4$  alkenyl radical or together for a  $C_1$ - $C_3$  alkylidene group,

$R^{15}$  and  $R^{16}$  stand for a common bond, and  $R^{16'}$  stands for a hydrogen atom or a  $C_1$ - $C_3$  alkyl radical, or

$R^{15}$  and  $R^{16}$  together stand for a ring of partial formula



in which  $n = 1$  and  $2$ , and  $X$  means a methylene group or an oxygen atom, and

$R^{16'}$  stands for a hydrogen atom,

$R^{171}$  stands for a hydrogen atom or a  $C_1-C_3$  alkyl radical,

$R^{172}$  stands for a hydrogen atom, a  $C_1-C_3$  alkyl radical, or a  $C_2-C_4$  alkenyl radical,

$R^{171'}$  and  $R^{172'}$  in each case stand for a hydrogen atom or for a common bond,

$R^{21}$  stands for a hydrogen atom or a  $C_1-C_3$  alkyl radical,

$R^{21'}$  stands for a hydrogen atom, a  $C_1-C_3$  alkyl radical, or a hydroxy group.

The wavy lines  $\diagup\diagdown\diagup\diagdown$  in the general formulas of this invention mean that the substituent in question can be found in  $\alpha$ - or  $\beta$ -position at the corresponding carbon atom.

The  $C_1-C_3$  alkyl groups that are mentioned above as possible substituents can be a methyl, ethyl, n-propyl or i-propyl group, and the  $C_1-C_4$  alkyl groups in addition can be an n-butyl, i-butyl or tert-butyl group. A methyl group or ethyl group is preferred in all cases.

In the case of the  $C_2-C_4$  alkenyl radical for  $R^{16}$ ,  $R^{16'}$  and/or  $R^{172}$ , this is a vinyl, allyl or but-3-enyl radical; the vinyl radical is preferred.

#### Special Gestagens:

Preferred according to this invention are combinations that consist of at least one gestagen and a  $\beta$ -cyclodextrin or  $\gamma$ -cyclodextrin, or derivatives of these cyclodextrins, which are

obtained by etherification or esterification of free alcoholic functions of cyclodextrins,

whereby the gestagens belong to the group of formula I:

in which

$R^3$  stands for an oxygen atom or two hydrogen atoms, and/or

$R^6$  stands for a hydrogen atom or for an  $\alpha$ -position or  $\beta$ -position  $C_1$ - $C_4$  alkyl radical,

if  $R^{6'}$  and  $R^7$  represent hydrogen atoms, or else

$R^{6'}$  stands for a hydrogen, chlorine or bromine atom or for a  $C_1$ - $C_4$  alkyl radical,

if  $R^{6'}$  and  $R^7$  represent a common additional bond, and/or

$R^{16}$  and  $R^{16'}$  in each case stand for a hydrogen atom, in each case for a methyl group or one of these two substituents stands for a  $C_1$ - $C_4$  alkyl group or a vinyl group, and the other of these two substituents stands for a hydrogen atom, or both together form a  $C1$ - $C3$ -alkenyl group, and/or

$R^{171}$  and  $R^{172}$ , independently of one another, stand for a hydrogen atom or a methyl group, and/or

$R^{171'}$  and  $R^{172'}$  in each case stand for a hydrogen atom or a common bond, and/or

$R^{21}$  stands for a hydrogen atom or a  $C_1$ - $C_3$  alkyl radical, and  $R^{21'}$  stands for a hydrogen atom or a hydroxy group,

and the other substituents all can have the meanings that are indicated in formula (I).

TOP SECRET 20440860

More preferred are combinations that consist of at least one gestagen and a  $\beta$ -cyclodextrin or  $\gamma$ -cyclodextrin, or derivatives of these cyclodextrins, which are obtained by etherification or esterification of free alcoholic functions of the cyclodextrins, whereby the gestagen belongs to the group of the following substances:

14,17-Ethano-19-norpregna-4,9-diene-3,20-dione;  
 14,17-ethano-19-norpregna-4,6-diene-3,20-dione;  
 14,17-ethano-19-norpregna-4,15-diene-3,20-dione  
 14,17-ethano-19-norpregna-4,6,15-triene-3,20-dione  
 14,17-ethano-19-norpregna-4,9,15-triene-3,20-dione  
 21-methyl-14,17-ethano-19-norpregn-4-ene-3,20-dione;  
 21-methyl-14,17-ethano-19-norpregna-4,9-diene-3,20-dione;  
 21-methyl-14,17-ethano-19-norpregna-4,6-diene-3,20-dione;  
 21-methyl-14,17-ethano-19-norpregna-4,15-diene-3,20-dione  
 21-methyl-14,17-ethano-19-norpregna-4,9,15-triene-3,20-dione  
 14,17-etheno-19-norpregn-4-ene-3,20-dione;  
 14,17-etheno-19-norpregna-4,6-diene-3,20-dione;  
 14,17-etheno-19-norpregna-4,9-diene-3,20-dione;  
 21-methyl-14,17-etheno-19-norpregn-4-ene-3,20-dione  
 21-methyl-14,17-etheno-19-norpregna-4,6-diene-3,20-dione  
 21-methyl-14,17-etheno-19-norpregna-4,9-diene-3,20-dione;  
 21-methyl-14,17-etheno-19-norpregna-4,9,11-triene-3,20-dione  
 21-hydroxy-14,17-etheno-19-norpregn-4-ene-3,20-dione  
 21-hydroxy-14,17-etheno-19-norpregna-4,9-diene-3,20-dione  
 17<sup>1</sup>-methyl-14,17-etheno-19-norpregn-4-ene-3,20-dione  
 17<sup>1</sup>-methyl-14,17-etheno-19-norpregna-4,6-diene-3,20-dione

dione



(17<sup>2</sup>R) -17<sup>2</sup>-methyl-14,17-ethano-19-norpregn-4-ene-3,20-dione

(17<sup>2</sup>R) -17<sup>2</sup>-methyl-14,17-ethano-19-norpregna-4,6-diene-3,20-dione

(17<sup>2</sup>R) -17<sup>2</sup>-methyl-14,17-ethano-19-norpregna-4,9-diene-3,20-dione

(17<sup>2</sup>R) -17<sup>2</sup>,21-dimethyl-14,17-ethano-19-norpregna-4,6-diene-3,20-dione

(17<sup>2</sup>R) -17<sup>2</sup>,21-dimethyl-14,17-ethano-19-norpregna-4,9-diene-3,20-dione

(17<sup>2</sup>R) -17<sup>2</sup>,21-dimethyl-14,17-ethano-19-norpregna-4,9,11-triene-3,20-dione

16-methylene-14,17-ethano-19-norpregn-4-ene-3,20-dione

16-methylene-14,17-ethano-19-norpregna-4,6-diene-3,20-dione

16-methylene-14,17-ethano-19-norpregna-4,9-diene-3,20-dione

21-hydroxy-14,17-ethano-19-norpregn-4-ene-3,20-dione;

21-hydroxy-14,17-ethano-19-norpregna-4,6-diene-3,20-dione;

21-hydroxy-14,17-ethano-19-norpregna-4,9-diene-3,20-dione;

21-hydroxy-14,17-ethano-19-norpregna-4,9,15-triene-3,20-dione

(21R) -21-hydroxy-21-methyl-14,17-ethano-19-norpregn-4-ene-3,20-dione;

(21S) -21-hydroxy-21-methyl-14,17-ethano-19-norpregn-4-ene-3,20-dione;

(21R) -21-hydroxy-21-methyl-14,17-ethano-19-norpregna-4,9-diene-3,20-dione;

(21S) -21-hydroxy-21-methyl-14,17-ethano-19-norpregna-4,9-diene-3,20-dione;

{

FOUO 2014.08.20

(21R)-21-hydroxy-21-methyl-14,17-ethano-18a-homo-19-norpregna-4,6-ene-3,20-dione

(21S)-21-hydroxy-21-methyl-14,17-ethano-18a-homo-19-norpregna-4,6-ene-3,20-dione

#### Effectiveness of the Combination:

After oral administration, an equilibrium develops between the non-dissociated complex and the individual components at the gastrointestinal resorption site from the complex that consists of gestagen and a sugar derivative. In this case, by displacement of the gestagen from the complexing sugar derivative, the free active ingredient is quickly released and then resorbed. The sugar derivative, however, is not resorbed and is excreted unchanged via the intestine. The pharmacological effectiveness of the gestagen is described in WO096/20209.

In the gestagen receptor-binding test on gestagenic action with use of cytosol that consists of rabbit uterus homogenate and <sup>3</sup>H-progesterone as a reference substance, the gestagen shows a very strong affinity to the gestagen receptor. In the pregnancy maintenance test on the rat, the gestagens of general formula (I) show a very high gestagenic action.

In addition to very high gestagenic action in the pregnancy maintenance test, the gestagens of general formula I, in contrast to the already known compound 14,17-ethano-19-norpregn-4-ene-3,20-dione, however, for the most part also show a good gestagenic action after oral administration.

Based on their high gestagenic action, the gestagens of general formula (I) can be used, for example, by themselves or combined with estrogens in contraceptive preparations. All other

The new combinations that consist of at least one gestagen of formula I and a  $\beta$ -cyclodextrin or  $\gamma$ -cyclodextrin, or derivatives of these cyclodextrins, can also be used in preparations for treating gynecological disorders and for substitution therapy. Because of their advantageous action profile, the combinations according to the invention are

especially well suited for treatment of premenstrual symptoms, such as headaches, depression, water retention and mastodynia. The daily dose in the treatment of premenstrual symptoms is approximately, for example, 1 to 20 mg, calculated as a free gestagen.

Finally, the new combinations can be used also as gestagenic components in the compositions that have become known recently for female birth control, which are distinguished by the additional use of a competitive progesterone antagonist (H. B. Croxatto and A. M. Salvatierra in Female Contraception and Male Fertility Regulation, ed. by Runnebaum, Rabe & Kiesel -- Vol. 2, Advances in Gynecological and Obstetric Research Series, Parthenon Publishing Group - 1991, page 245).

The dose lies in the range already indicated, and the formulation can be carried out as in conventional OC-preparations. The administration of the additional, competitive progesterone antagonist can also be performed sequentially in this case.

The formulation of the pharmaceutical preparations based on the new combinations is carried out in a way that is known in the art, by the active ingredient, optionally in combination with an estrogen, being processed with the vehicles, diluents, optionally flavoring correctives, etc., that are commonly used in galenicals and being converted into the desired form of administration.

For the preferred oral administration, especially tablets, coated tablets, capsules, pills, suspensions or solutions are suitable.

09807492-080301

For the transdermal administration, especially matrix or membrane patches are suitable.

The combinations with compounds of general formula (I) can also be administered continuously by an intrauterine release system (IUD); the release rate of the active compound(s) is selected in this case so that the daily released dose lies within the dose ranges already indicated.

The production of the gestagens is described in more detail in WO 96/20209 (publication date July 4, 1996).

Preferred is a combination with the gestagen (21S)-21-hydroxy-21-methyl-14,17-ethano-19-norpregna-4,9,15-triene-3,20-dione.

#### Cyclodextrins:

$\beta$ -Cyclodextrin,  $\gamma$ -cyclodextrin and derivatives of these cyclodextrins, which are obtained by etherification or esterification of free alcoholic functions of cyclodextrins, are described in J. Pharm. Sci. 74 (1985), pp. 987-990 or Int. J. Pharm. 29 (1986), pp. 73-82.

More preferred is a combination that consists of a gestagen and a cyclodextrin, whereby the cyclodextrin is a  $\beta$ -cyclodextrin.

Most preferred is the combination that consists of the gestagen (21S)-21-hydroxy-21-methyl-14,17-ethano-19-norpregna-4,9,15-triene-3,20-dione and  $\beta$ -cyclodextrin.

09807402 20420860

### Advantages:

If gestagens, especially (21S)-21-hydroxy-21-methyl-14,17-ethano-19-norpregna-4,9,15-triene-3,20-dione, are mixed with adjuvants such as lactose, corn starch, mannitol, microcrystalline cellulose, polyvidone, hydroxypropylmethyl cellulose, dicalcium phosphate and maltodextrin, an accelerated degradation can be noted. In this connection, this is an acyloin rearrangement. There results a mixture that consists of two pairs of diastereomers with respectively exchanged positions of the keto group and the hydroxyl group at the C<sub>20</sub> and C<sub>21</sub> atom. From the four possible structures, only one corresponds to the above-mentioned substance (21S)-21-hydroxy-21-methyl-14,17-ethano-19-norpregna-4,9,15-triene-3,20-dione.

When stored at 25°C (60% relative humidity) over 3 months, the content of non-complexed (21S)-21-hydroxy-21-methyl-14,17-ethano-19-norpregna-4,9,15-triene-3,20-dione drops to below 90% of the starting value, if the substance is pelletized (i) either with the adjuvants lactose, corn starch, modified corn starch, polyvidone 25,000 and magnesium stearate (ii) or with the adjuvants with mannitol, hydroxypropylmethyl cellulose and magnesium stearate. The formulations of mannitol that can be pelletized directly with adjuvants (iii) or (iv) microcrystalline cellulose and magnesium stearate or (v) glyceryltribehenate also show a comparable degradation of the substance (21S)-21-hydroxy-21-methyl-14,17-ethano-19-norpregna-4,9,15-triene-3,20-dione.

By the combination according to the invention (complexing of the gestagen with  $\beta$ -cyclodextrin), tablets can be obtained that

despite storage at critical temperatures have an active ingredient content that is still over 90% of the starting value in an open storage jar after 6 months of storage at 40°C, 75% relative humidity.

#### Additional Embodiments with Regard to Cyclodextrins

Advantageous is a combination according to the invention in which the cyclodextrin and the gestagen

are present with  $\beta$ -cyclodextrin in a complex of 1:n

(gestagen : cyclodextrin,  $n \geq 1$ ), a ratio of 1:2 (gestagen : cyclodextrin) is preferred, and

are present with  $\gamma$ -cyclodextrin also in a complex of 1:n ( $n \geq 1$ ) (gestagen : cyclodextrin); a ratio of 1:2 (gestagen : cyclodextrin) is preferred.

In addition to the increased shelf life, the stoichiometry of the complexing can be determined. In this case, it is obvious that the complexing in complexes (21S)-21-hydroxy-21-methyl-14,17-ethano-19-norpregna-4,9,15-triene-3,20-dione and  $\gamma$ -cyclodextrin takes place at a ratio of 1:1 to 1:2 (gestagen : cyclodextrin). A complexing ratio of 1:2 (gestagen : cyclodextrin) is advantageous.

In the complex that consists of (21S)-21-hydroxy-21-methyl-14,17-ethano-19-norpregna-4,9,15-triene-3,20-dione and  $\beta$ -cyclodextrin, a ratio of 1:2 (gestagen : cyclodextrin) is present.

00007402-000001



Such complexes have a sometimes lower solubility product than the steroid by itself. The complexes thus can be produced by a precipitation reaction (e.g., co-precipitation).

#### **Additional Embodiments as Pharmaceutical Agents**

The combination according to the invention is preferred as a pharmaceutical agent. The action of the substances is described above (cf. WO96/20209).

More preferred is a pharmaceutical agent or a pharmaceutical preparation that contains a combination according to the invention, including pharmaceutical vehicles and adjuvants.

Still more preferred is a pharmaceutical agent or pharmaceutical preparation that contains a combination according to the invention for peroral, oral, parenteral, transdermal, pulmonary, nasal, rectal, vaginal or intrauterine use.

In addition, the invention relates to the use of the combinations according to the invention together with pharmacological adjuvants and vehicles, which are physiologically compatible, for the production of a medication for treating menopausal symptoms. Such adjuvants and vehicles are described in Remington's Pharmaceutical Science, 15th Ed. Mack Publishing Company, Easton, Pennsylvania (1980).

The combinations according to the invention show the action in the above-mentioned test at concentrations of 0.1 to 1000 ng/ml of the gestagen.

For the therapeutic action, the suitable dose is different and depends on, for example, the combinations that are used with

gestagens of general formula I, the host, the type of administration, and the type and the severity of the conditions to be treated. In general, however, satisfactory results can be expected in animals with daily doses of gestagens of 1 to 3000  $\mu\text{g/kg}$  of animal body weight. In the case of larger mammals, for example humans, a recommended daily dose of gestagen is 0.1 to 200 mg. Preferred are values of 0.3 to 60 mg per day, more preferred 1 to 20 mg per day and most preferred 2 to 10 mg per day.

The invention additionally provides

- (i) The use of one of the combinations according to the invention for the production of a medication for treating menopausal symptoms;
- (ii) A process for treating menopausal symptoms; said process comprises an administration of a combination amount according to the invention, whereby the amount suppresses the disease, and whereby the combination amount is given to a patient who requires such a medication;
- (iii) a pharmaceutical composition for treating menopausal symptoms; said treatment comprises one of the combinations according to the invention and at least one pharmaceutical adjuvant and/or vehicle.

The invention additionally provides

- (i) The use of one of the combinations according to the invention for the production of a medication for

20250420 10:00:00

(ii) a process for treating premenstrual symptoms, such as headaches, depression, water retention and mastodynia; said process comprises an administration of a combination amount according to the invention, whereby the amount suppresses the disease, and whereby the combination amount is given to a patient who requires such a medication;

The daily dose in the treatment of premenstrual symptoms is approximately 1 to 20 mg, calculated as a free gestagen.

The invention comprises a combination according to the invention for birth control.

Based on their high gestagenic action, the new combinations can be used with gestagens of general formula (I), for example by themselves or combined with estrogens in preparations for contraception. All other possible uses that are known for gestagens are also now options for the new compounds, however.

The dose of the combination according to the invention in contraceptive preparations is preferably to be 0.01 to 2 mg per day, calculated as free gestagen.

The gestagenic and estrogenic active ingredient components are preferably administered orally together in contraceptive preparations. The daily dose is preferably administered one time.

As estrogens, preferably synthetic estrogens such as ethinylestradiol,  $14\alpha,17\alpha$ -ethano-1,3,5(10)-estratriene-3,17 $\beta$ -diol (WO 88/01275) or  $14\alpha,17\alpha$ -ethano-1,3,5(10)-estratriene-3,16 $\alpha,17\beta$ -triol (WO 91/08219) are considered.

The estrogen is administered in an amount that corresponds to that of 0.01 to 0.05 mg of ethinylestradiol.

Finally, the new combinations can also be used as gestagenic components in the compositions that have become known recently for female birth control, which are distinguished by the additional use of a competitive progesterone antagonist (H. B. Croxatto and A. M. Salvatierra in Female Contraception and Male Fertility Regulation, ed. by Runnebaum, Rabe & Kiesel -- Vol. 2, Advances in Gynecological and Obstetric Research Series, Parthenon Publishing Group - 1991, page 245).

The dose lies in the range already indicated, and the formulation can be carried out as in conventional OC-preparations. The administration of the additional, competitive progesterone antagonist can also be performed sequentially in this case.

08807402-08807402

## Additional Embodiments as Stabilizing Processes

Advantageous is a process for stabilizing a gestagen according to Formula I with use of a  $\beta$ -cyclodextrin or  $\gamma$ -cyclodextrin or derivatives of these cyclodextrins, which are obtained by etherification or esterification of free alcoholic functions of the cyclodextrins. The preferred complex that consists of gestagen and cyclodextrin is the complex that consists of (21S)-21-hydroxy-21-methyl-14,17-ethano-19-norpregna-4,9,15-triene-3,20-dione and  $\beta$ -cyclodextrin.

Preferred is a process for complexing a gestagen and a  $\beta$ -cyclodextrin or  $\gamma$ -cyclodextrin while being triturated as a dry mixture. X-ray spectra of the powder, which was produced as a dry mixture, show that the complexing is already partially present but has not finished. This complexing is already surprising as a dry mixture.

More preferred is the production of complexes by precipitation reaction, e.g., co-precipitation, by an ethanolic solution of the gestagen being added in drops to an aqueous cyclodextrin solution. The complexes that consist of gestagens and cyclodextrin and that are produced by precipitation can be brought into the desired particle size distribution before being turned into pharmaceutical agents by suitable grinding techniques, e.g., that of air-jet grinding.

Preferred for production of the formulation is an encapsulation or granulation and subsequent pelletizing.

More preferred is a process for the direct pelletizing of the complex that consists of a gestagen with  $\beta$ -cyclodextrin or  $\gamma$ -

cyclodextrin with the addition of pharmaceutically compatible adjuvants. In this case, a granulation step is eliminated. A granulation step involves the risk of the cyclodextrin complex being destroyed by the steroid being displaced from the cyclodextrin host by adjuvant molecules as guests.

Direct pelletizing was therefore performed with the addition of adjuvants of microcrystalline cellulose, lactose, croscarmellose-Na, highly dispersed silicon dioxide and magnesium stearate.

20140400

### Example

The complexes that consist of (21S)-21-hydroxy-21-methyl-14,17-ethano-19-norpregna-4,9,15-triene-3,20-dione and  $\beta$ -cyclodextrin and  $\gamma$ -cyclodextrin were produced in the following way:

19 mmol of the cyclodextrin was dissolved in 610 ml of water that is 45°C, and within 30 minutes, 7.6 mmol of ZK 187226, dissolved in 10 ml of ethanol, was added in drops. With another 5 ml of ethanol, it was flushed, allowed to cool to room temperature, stirred for 24 hours at room temperature, stirred for 2 hours in an ice bath (2°C), and the precipitate was suctioned off via a G2-frit. The complex that was obtained was then washed 2 more times with 50 ml of ice water each and once with ice-cold acetone. After drying in a desiccator on phosphorus pentoxide, the complex was characterized by Karl-Fischer-water determination, HPLC, DSC and x-ray powder diffractomy.

The fact that it is only after comparative trituration that a clear change is observed both in the x-ray powder spectrum and in the DSC indicates that a partial, but incomplete complexing already takes place in the trituration of (21S)-21-hydroxy-21-methyl-14,17-ethano-19-norpregna-4,9,15-triene-3,20-dione with  $\beta$ -cyclodextrin or  $\gamma$ -cyclodextrin.

After the complexes were ground, tablets were now produced from the produced cyclodextrin complexes of (21S)-21-hydroxy-21-methyl-14,17-ethano-19-norpregna-4,9,15-triene-3,20-dione. For pelletizing, it is important that it is performed as direct

20240420

pelletizing, without a granulation step. Such a granulation process would namely involve the risk of the cyclodextrin complexes being destroyed by (21S)-21-hydroxy-21-methyl-14,17-ethano-19-norpregna-4,9,15-triene-3,20-dione being displaced from the cyclodextrin host by adjuvant molecules as guests.

Direct pelletizing would therefore be performed with the addition of adjuvants of microcrystalline cellulose, lactose, croscarmellose-Na, highly dispersed silicon dioxide and magnesium stearate.

The tablets that are produced as well as a formulation that is produced from non-complexed active ingredient and the complexes that consist of (21S)-21-hydroxy-21-methyl-14,17-ethano-19-norpregna-4,9,15-triene-3,20-dione and  $\beta$ -cyclodextrin and  $\gamma$ -cyclodextrin were stored to test shelf life, and the content of (21S)-21-hydroxy-21-methyl-14,17-ethano-19-norpregna-4,9,15-triene-3,20-dione (in the tablets relative to the nominal content of 0.1 mg of active ingredient per tablet, in the complexes as percent by weight) was determined after 1.5-month and 3-month storage. The results are shown in Tables 1 to 5.

In comparison to the tablets produced with an uncomplexed active ingredient, the tablets produced from the  $\beta$ -cyclodextrin clathrates and  $\gamma$ -cyclodextrin clathrates show a considerably improved shelf life. The  $\beta$ -cyclodextrin clathrate shows the best stabilization, can be produced in good quality and is also economically more advantageous compared to  $\gamma$ -cyclodextrin. Based on the results of the 3-month storage, an adequate shelf life for a market formulation results for the tablets that are produced

000007402-00000



with the complex that consists of (21S)-21-hydroxy-21-methyl-14,17-ethano-19-norpregna-4,9,15-triene-3,20-dione and  $\beta$ -cyclodextrin.

**Table 1:  $\beta$ -Cyclodextrin-Clathrate Tablets**

Monate	-18°C	+25°C	+25°C, 60% r.F.	+40°C	+40°C, 75% r.F.	+60°C	+60°C, 75% r.F.
0	97.0% (1.0%)	-	-	-	-	-	-
1.5	97.4% (0.8%)	97.0% (0.6%)	96.7% (0.7%)	95.5% (1.8%)	93.5% (0.9%)	92.9% (0.7%)	89.7% (0.8%)
3	97.0% (0.8%)	97.1% (1.0%)	96.6% (0.7%)	95.2% (0.5%)	91.8% (1.0%)	92.6% (1.2%)	89.0% (1.7%)

[Key to Table 1:]

Monate = months

60% r.F. = relative atmospheric humidity

10E030-20420860

**Table 2:  $\gamma$ -CD-Clathrate Tablets**

Monate	-18°C	+25°C	+25°C, 60% r.F.	+40°C	+40°C, 75% r.F.	+60°C	+60°C, 75% r.F.
0	93.0% (8.3%)	-	-	-	-	-	-
1.5	97.9% (2.6%)	99.4% (2.5%)	98.8% (2.7%)	98.5% (3.6%)	95.1% (7.3%)	90.0% (4.7%)	85.1% (5.1%)
3	99.8% (4.2%)	96.5% (3.9%)	99.9% (5.7%)	97.9% (3.4%)	88.7% (3.0%)	77.1% (4.7%)	79.1% (1.6%)

[Key to Table 2:]

Monate = months

r.F. = relative atmospheric humidity

**Table 3: (21S)-21-Hydroxy-21-methyl-14,17-ethano-19-norpregna-4,9,16-triene-3,20-dione Tablets**

Monate	-18°C	+25°C	+25°C, 60% r.F.	+40°C	+40°C, 75% r.F.	+60°C	+60°C, 75% r.F.
0	100.1% (0.8%)	-	-	-	-	-	-
1.5	nicht untersucht	90.6% (0.5%)	80.3% (0.3%)	26.6% (0.8%)	27.9% (1.1%)	0.3% (1.7%)	0.1% (14.3%)
3	101.2% (0.5%)	80.1% (0.6%)	63.9% (1.0%)	8.5% (5.2%)	14.1% (4.1%)	0.3% (68.0%)	0.1% (65.6%)

TEEBD 204.0860

nicht untersucht = not examined

[illegible]

Monate	-18°C	+25°C	+25°C, 60% r.F.	+40°C	+40°C, 75% r.F.	+60°C	+60°C, 75% r.F.
0	12.5% (0.3%)	-	-	-	-	-	-
1.5	12.5% (0.7%)	nicht untersucht	12.5% (0.4%)	nicht untersucht	12.4% (0.9%)	nicht untersucht	12.3% (0.8%)
3	12.5% (0.5%)	nicht untersucht	12.5% (0.3%)	nicht untersucht	12.6% (0.3%)	nicht untersucht	12.3% (0.5%)

nicht untersucht = not examined

**Table 5:** (21S)-21-Hydroxy-21-methyl-14,17-ethano-19-norpregna-4,9,15-triene-3,20-dione- $\gamma$ -cyclodextrin Complex Content in %

Monate	-18°C	+25°C	+25°C, 60% r.F.	+40°C	+40°C, 75% r.F.	+60°C	+60°C, 75% r.F.
0	13.6% (2.8%)	-	-	-	-	-	-
1.5	13.8% (1.2%)	nicht untersucht	13.7% (0.8%)	nicht untersucht	13.3% (0.5%)	nicht untersucht	12.0% (1.3%)
3	13.9% (2.5%)	nicht untersucht	13.5% (1.3%)	nicht untersucht	13.0% (0.5%)	nicht untersucht	10.0% (1.1%)

r.F. = relative atmospheric humidity, set in the climatic chamber

[Key to Table 5:]

Monate = months

r.F. = relative atmospheric humidity

nicht untersucht = not examined

REF ID: A61236